8EHQ_1004_15708

noveon.

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Kenneth J. Willings
Vice President
Health, Safety & Environmental

September 28, 2004

CONTAINS NO CBI

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Document Processing Center (7407)
Attention: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Avenue, N.W.
Washington, DC 20460-0001

Re: TSCA 8(e) Submission of 2-Ethylhexyl Phosphate Acute Oral Toxicity Study

Dear Sir or Madam:

Noveon, Inc. (Noveon) submits this letter pursuant to Section 8(e) of the Toxic Substance Act (TSCA) to inform EPA of the findings of an acute oral toxicity study on 2-ethylhexyl phosphate. Noveon has not made a determination as to whether a significant risk of injury to health is actually presented by the findings.

2-Ethylhexyl phosphate (CAS# 12645-31-7) is listed by EPA as a High Production Volume (HPV) Chemical. The acute oral toxicity study identified certain clinical signs that EPA believes can be evidence of neurotoxicity. In view of these findings, Noveon has elected to inform the EPA.

The draft report is enclosed. The final report will be provided when it is available

None of the information in this submission is claimed as confidential business information.

If you have any questions, please contact Dr. Robert K. Hinderer at 216-447-5181 or robert.hinderer@noveon.com.

Sincerely,

Kenneth J. Willings

Kenneth J. Willings
Vice President HS&E

cc: Robert K. Hinderer, Ph.D.

8EHQ-04-15708

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SafePharm Laboratories

**OS 197965:**

# ACUTE ORAL TOXICITY IN THE RAT - ACUTE TOXIC CLASS METHOD

**SPL PROJECT NUMBER: 525/591**

**AUTHOR:** A Sanders

**STUDY SPONSOR:**

The Lubrizol Corporation
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OHIO 44092-2298
UNITED STATES OF AMERICA

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## QUALITY ASSURANCE REPORT

This study type is classed as short-term. The standard test method for this study type ("General Study Plan" in OECD terminology) was reviewed for compliance once only on initial production. Inspection of the routine and repetitive procedures that constitute the study is carried out as a continuous process designed to encompass the major phases at or about the time this study was in progress.

This report has been audited by Safepharm Quality Assurance Unit, and is considered to be an accurate account of the data generated and of the procedures followed.

In each case, the outcome of QA evaluation is reported to the Study Director and Management on the day of evaluation. Audits of study documentation, and process inspections appropriate to the type and schedule of this study were as follows:

| | | |
|---|---|---|
| | 07 June 2002 | Standard Test Method Compliance Audit |
| | 14 July 2004 | Test Material Preparation |
| | 22 July 2004 | Animal Preparation |
| | 14 July 2004 | Dosing |
| | 15 July 2004 | Assessment of Response |
| | 22 July 2004 | Necropsy |
| § | 24 August 2004 | Draft Report Audit |
| § | Date of QA Signature | Final Report Audit |

§ Evaluation specific to this study

..... DATE: .....

For Safepharm Quality Assurance Unit*

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***Authorised QA Signatures:**

| | |
|---|---|
| Head of Department: | JR Pateman CBiol MIBiol DipRQA AIQA FRQA |
| Deputy Head of Department: | JM Crowther MIScT MRQA |
| Senior Audit Staff: | JV Johnson BSc MRQA; G Wren ONC MRQA |

## GLP COMPLIANCE STATEMENT

The work described was performed in compliance with UK GLP standards (Schedule 1, Good Laboratory Practice Regulations 1999 (SI 1999/3106 as amended by SI 2004/0994)). These Regulations are in accordance with GLP standards published as OECD Principles on Good Laboratory Practice (revised 1997, ENV/MC/CHEM(98)17); and are in accordance with, and implement, the requirements of Directives 2004/9/EC and 2004/10/EC.

These international standards are acceptable to the Regulatory agencies of the following countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Republic of Korea, Luxembourg, Mexico, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States of America.

This report fully and accurately reflects the procedures used and data generated.

..... DATE: .....

A Sanders
Study Director

## CONTENTS

## OS 197965:

## ACUTE ORAL TOXICITY IN THE RAT – ACUTE TOXIC CLASS METHOD

## SUMMARY

***Introduction.*** The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 17 December 2001)

***Method.*** A group of three fasted females was treated with the test material at a dose level of 2000 mg/kg bodyweight. Based on the results from this dose level further groups of fasted females were treated at a dose level of 300 mg/kg bodyweight. Dosing was performed sequentially.

The test material was administered orally undiluted for the 2000 mg/kg dose level and orally as a solution in arachis oil BP for the 300 mg/kg dose level. Clinical signs and bodyweight development were monitored during the study. All animals were subjected to gross necropsy.

***Mortality.*** Two animals treated at a dose level of 2000 mg/kg were found dead one or two days after dosing. There were no deaths noted in animals treated at a dose level of 300 mg/kg.

***Clinical Observations.*** Signs of systemic toxicity noted in animals treated at a dose level of 2000 mg/kg were hunched posture, lethargy, pilo-erection, diarrhoea, diuresis, dehydration, ataxia, emaciation, decreased respiratory rate, laboured respiration and tiptoe gait. The surviving animal treated at a dose level of 2000 mg/kg appeared normal four days after dosing. There were no signs of systemic toxicity noted in animals treated at a dose level of 300 mg/kg.

***Bodyweight.*** The surviving animals showed expected gains in bodyweight over the study period.

***Necropsy.*** Abnormalities noted at necropsy of animals that died during the study were haemorrhagic lungs, dark liver, dark kidneys, epithelial sloughing and pale gastric mucosa and epithelial sloughing and pale non-glandular region of the stomach. No abnormalities were noted at necropsy of animals that were killed at the end of the study.

***Conclusion.*** The acute oral median lethal dose ($LD_{50}$) of the test material in the female Sprague-Dawley CD strain rat was estimated to be in the range of 500 - 1000 mg/kg bodyweight.

# OS 197965:

# ACUTE ORAL TOXICITY IN THE RAT - ACUTE TOXIC CLASS METHOD

## 1. INTRODUCTION

The study was performed to assess the acute oral toxicity of the test material following a single oral administration in the Sprague-Dawley CD strain rat. The method was designed to meet the requirements of the following:

- OECD Guidelines for the Testing of Chemicals No. 423 "Acute Oral Toxicity – Acute Toxic Class Method" (adopted 17 December 2001)

The rat was selected for this study as it is a readily available rodent species, historically used in safety evaluation studies, and is acceptable to appropriate regulatory authorities. The oral route was selected as the most appropriate route of exposure and the results are believed to be of value in predicting the likely toxicity of the test material to man.

The study was performed between 01 July 2004 and 27 July 2004.

## 2. TEST MATERIAL AND EXPERIMENTAL PREPARATION

### 2.1 Description, Identification and Storage Conditions

| | | |
|---|---|---|
| Sponsor's identification | : | OS 197965 |
| Mono-ester ratio | : | 39-51% |
| Di-ester ratio | : | 45-63% |
| Description | : | extremely pale yellow slightly viscous liquid |
| Date received | : | 24 May 2004 |
| Storage conditions | : | room temperature in the dark |

The integrity of supplied data relating to the identity, purity and stability of the test material is the responsibility of the Sponsor.

### 2.2 Preparation of Test Material

For the purpose of the 2000 mg/kg dose level the test material was used as supplied. The specific gravity was determined and used to calculate the appropriate dose volume for the required dose level.

For the purpose of the 300 mg/kg dose level the test material was freshly prepared, as required, as a solution at the appropriate concentration in arachis oil BP. Arachis oil BP was used because the test material did not dissolve/suspend in distilled water.

Determination by analysis of the concentration, homogeneity and stability of the test material preparations was not appropriate because it was not specified in the Study Plan and is not a requirement of the Test Guideline.

## 3. METHODS

### 3.1 Animals and Animal Husbandry

Female Sprague-Dawley CD (Crl: CD® (SD) IGS BR) strain rats were supplied by Charles River (UK) Ltd, Margate, Kent, UK. On receipt the animals were randomly allocated to cages. The animals were nulliparous and non-pregnant. After an acclimatisation period of at least five days the animals were selected at random and given a number unique within the study by indelible ink-marking on the tail and a number written on a cage card. At the start of the study the animals were eight to twelve weeks of age. The bodyweights fell within an interval of ± 20% of the mean initial bodyweight of the first treated group.

The animals were housed in groups of three in suspended solid-floor polypropylene cages furnished with woodflakes. With the exception of an overnight fast immediately before dosing and for approximately three to four hours after dosing, free access to mains drinking water and food (Certified Rat and Mouse Diet (Code 5LF2) supplied by BCM IPS Limited, London, UK) was allowed throughout the study. The diet, drinking water and bedding were routinely analysed and were considered not to contain any contaminants that would reasonably be expected to affect the purpose or integrity of the study.

The temperature and relative humidity were set to achieve limits of 19 to 25°C and 30 to 70% respectively. Any occasional deviations from these targets were considered not to have affected the purpose or integrity of the study. The rate of air exchange was at least fifteen changes per hour and the lighting was controlled by a time switch to give twelve hours continuous light (06:00 to 18:00) and twelve hours darkness.

The animals were provided with environmental enrichment items which were considered not to contain any contaminant of a level that might have affected the purpose or integrity of the study.

## 3.2 Procedure

Using all available information on the toxicity of the test material, 2000 mg/kg was chosen as the starting dose.

Groups of fasted animals were treated as follows:

| Dose Level (mg/kg) | Specific Gravity | Concentration (mg/ml) | Dose Volume (ml/kg) | Number of Rats |
|---|---|---|---|---|
| | | | | Female |
| 2000 | 1.013 | - | 1.98 | 3 |
| 300 | - | 30 | 10 | 3 |
| 300 | - | 30 | 10 | 3 |

- = Not applicable

All animals were dosed once only by gavage, using a metal cannula attached to a graduated syringe. The volume administered to each animal was calculated according to the fasted bodyweight at the time of dosing. Treatment of animals was sequential. Sufficient time was allowed between each group and each dose level to confirm the survival of the previously dosed animals.

The animals were observed for deaths or overt signs of toxicity ½, 1, 2 and 4 hours after dosing and subsequently once daily for up to fourteen days.

Individual bodyweights were recorded prior to dosing and seven and fourteen days after treatment or at death.

At the end of the observation period the surviving animals were killed by cervical dislocation. All animals were subjected to gross pathological examination. This consisted of an external examination and opening of the abdominal and thoracic cavities for examination of major organs. The appearance of any macroscopic abnormalities was recorded. No tissues were retained.

The sequence of dosing may not always follow the Test Guideline as shown in the schematic diagram in Appendix 1. It is Company Policy to minimise the number of animals used on each study in accordance with UK Government Home Office guidelines. The sequence of testing does not affect the final classification of the test material.

### 3.3 Evaluation of Data

Data evaluations included the relationship, if any, between the exposure of the animal to the test material and the incidence and severity of all abnormalities including behavioural and clinical observations, gross lesions, bodyweight changes, mortality and any other toxicological effects.

Using the mortality data obtained, an estimate of the acute oral median lethal dose ($LD_{50}$) of the test material was made as shown in the schematic diagram in Appendix 1.

## 4. ARCHIVES

Unless instructed otherwise by the Sponsor, all original data and the final report will be retained in the Safepharm archives for five years, after which instructions will be sought as to further retention or disposal.

# 5. RESULTS

## 5.1 Mortality Data

Individual mortality data are given in Table 1.

Two animals treated at a dose level of 2000 mg/kg were found dead one or two days after dosing.

There were no deaths noted in animals treated at a dose level of 300 mg/kg.

## 5.2 Clinical Observations

Individual clinical observations are given in Table 2 and Table 3.

Signs of systemic toxicity noted in animals treated at a dose level of 2000 mg/kg were hunched posture, lethargy, pilo-erection, diarrhoea, diuresis, dehydration, ataxia, emaciation, decreased respiratory rate, laboured respiration and tiptoe gait. The surviving animal treated at a dose level of 2000 mg/kg appeared normal four days after dosing.

There were no signs of systemic toxicity noted in animals treated at a dose level of 300 mg/kg.

## 5.3 Bodyweight

Individual bodyweights and weekly bodyweight changes are given in Table 4 and Table 5.

The surviving animals showed expected gains in bodyweight over the study period.

## 5.4 Necropsy

Individual necropsy findings are given in Table 6 and Table 7.

Abnormalities noted at necropsy of animals that died during the study were haemorrhagic lungs, dark liver, dark kidneys, epithelial sloughing and pale gastric mucosa and epithelial sloughing and pale non-glandular region of the stomach. No abnormalities were noted at necropsy of animals that were killed at the end of the study.

# 6. CONCLUSION

The acute oral median lethal dose ($LD_{50}$) of the test material in the female Sprague-Dawley CD strain rat was estimated to be in the range of 500 - 1000 mg/kg bodyweight.

## 7. DISCUSSION

Primarily the effects noted are indicative of a strong gastric irritant and not a neurotoxicant. The macroscopic abnormalities noted at necropsy of the two moribund animals, treated at a dose level of 2000 mg/kg, would also appear to support this assessment; with epithelial sloughing and pale appearance of both the gastric mucosa and non-glandular region of the stomach.

The effects noted in the animal that survived at a dose level of 2000 mg/kg, in particular the tiptoe gait, were considered to be transient in nature and not due to neurotoxicity, as they were of relatively short duration and did not re-occur during the study period i.e. they were not intermittent.

The fact that the effects seen in this surviving animal were considered to be transient would also indicate the test material to be a strong gastric irritant rather than a neurotoxicant. There was no indication that permanent damage to the neural system was involved.

These types of findings are commonly observed on this type of study within this testing facility. The incidence and duration show no correlation with effects seen with known neurotxic materials.

**Table 1 Mortality Data**

| Dose Level mg/kg | Sex | Number of Animals Treated | Deaths During Day of Dosing (Hours) | | | | Deaths During Period After Dosing (Days) | | | | | | | | Deaths |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | ½ | 1 | 2 | 4 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8-14 | |
| 2000 | Female | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2/3 |
| 300 | Female | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0/3 |
| | Female | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0/3 |

**Table 2 Individual Clinical Observations - 2000 mg/kg**

| Dose Level mg/kg | Animal Number and Sex | Effects Noted After Dosing (Hours) | | | | Effects Noted During Period After Dosing (Days) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ½ | 1 | 2 | 4 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 2000 | 1-0 Female | 0 | 0 | 0 | HLP DuD | X | | | | | | | | | | | | | |
| | 1-1 Female | 0 | 0 | H | HLP DuD | HLPA DhRd RlWt Em | X | | | | | | | | | | | | |
| | 1-2 Female | 0 | 0 | 0 | HLP Du | HWt | HWt | H | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

0 = No signs of systemic toxicity
A = Ataxia
D = Diarrhoea
Dh = Dehydration
Du = Diuresis
Em = Emaciation
H = Hunched posture
L = Lethargy
P = Pilo-erection
Rd = Decreased respiratory rate
Rl = Laboured respiration
Wt = Tiptoe gait
X = Animal dead

**Table 3 Individual Clinical Observations - 300 mg/kg**

| Dose Level mg/kg | Animal Number and Sex | Effects Noted After Dosing (Hours) | | | | Effects Noted During Period After Dosing (Days) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ½ | 1 | 2 | 4 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 300 | 2-0 Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2-1 Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2-2 Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3-0 Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3-1 Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3-2 Female | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

0 = No signs of systemic toxicity

**Table 4 Individual Bodyweights and Weekly Bodyweight Changes - 2000 mg/kg**

| Dose Level mg/kg | Animal Number and Sex | Bodyweight (g) at Day | | | Bodyweight (g) at Death | Bodyweight Gain (g) During Week | |
|---|---|---|---|---|---|---|---|
| | | 0 | 7 | 14 | | 1 | 2 |
| 2000 | 1-0 Female | 195 | - | - | 178 | - | - |
| | 1-1 Female | 194 | - | - | 172 | - | - |
| | 1-2 Female | 194 | 214 | 228 | | 20 | 14 |

- = Animal dead

**Table 5 Individual Bodyweights and Weekly Bodyweight Changes - 300 mg/kg**

| Dose Level mg/kg | Animal Number and Sex | Bodyweight (g) at Day | | | Bodyweight Gain (g) During Week | |
|---|---|---|---|---|---|---|
| | | 0 | 7 | 14 | 1 | 2 |
| 300 | 2-0 Female | 215 | 261 | 274 | 46 | 13 |
| | 2-1 Female | 219 | 241 | 244 | 22 | 3 |
| | 2-2 Female | 220 | 251 | 276 | 31 | 25 |
| | 3-0 Female | 203 | 243 | 254 | 40 | 11 |
| | 3-1 Female | 211 | 252 | 272 | 41 | 20 |
| | 3-2 Female | 213 | 261 | 281 | 48 | 20 |

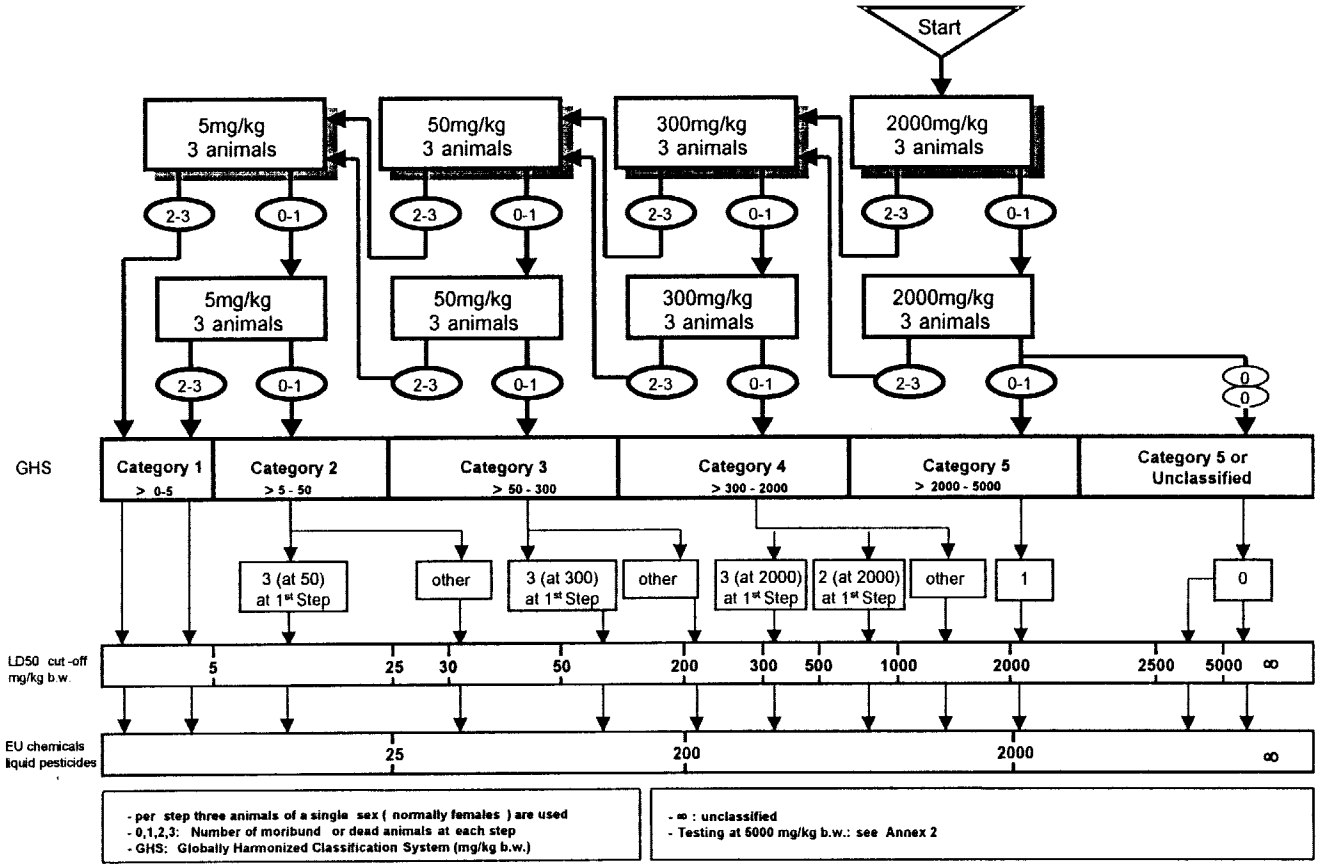
**Table 6 Individual Necropsy Findings - 2000 mg/kg**

| Dose Level mg/kg | Animal Number and Sex | Time of Death | Macroscopic Observations |
|---|---|---|---|
| 2000 | 1-0 Female | Found dead Day 1 | Lungs: haemorrhagic<br>Liver: dark<br>Kidneys: dark<br>Gastric mucosa: epithelial sloughing<br>: pale<br>Non-glandular region of the stomach: epithelial sloughing<br>: pale |
| | 1-1 Female | Found dead Day 2 | Lungs: haemorrhagic<br>Liver: dark<br>Kidneys: dark<br>Gastric mucosa: epithelial sloughing<br>: pale<br>Non-glandular region of the stomach: epithelial sloughing<br>: pale |
| | 1-2 Female | Killed Day 14 | No abnormalities detected |

**Table 7 Individual Necropsy Findings - 300 mg/kg**

| Dose Level mg/kg | Animal Number and Sex | Time of Death | Macroscopic Observations |
|---|---|---|---|
| 300 | 2-0 Female | Killed Day 14 | No abnormalities detected |
| | 2-1 Female | Killed Day 14 | No abnormalities detected |
| | 2-2 Female | Killed Day 14 | No abnormalities detected |
| | 3-0 Female | Killed Day 14 | No abnormalities detected |
| | 3-1 Female | Killed Day 14 | No abnormalities detected |
| | 3-2 Female | Killed Day 14 | No abnormalities detected |

## Appendix 1 Test Procedure with a Starting Dose of 2000 mg/kg Bodyweight



## Appendix 2 Statement of GLP Compliance in Accordance with Directive 88/320/EEC


### THE DEPARTMENT OF HEALTH OF THE GOVERNMENT OF THE UNITED KINGDOM

### GOOD LABORATORY PRACTICE

STATEMENT OF COMPLIANCE
IN ACCORDANCE WITH DIRECTIVE 88/320 EEC

LABORATORY
**SafePharm Limited**
**Shardlow Business Park,**
**London Road,**
**Shardlow,**
**Derbyshire,**
**DE72 2GD**

TEST TYPE
**Analytical/Clinical**
**Chemistry**
**Environmental tox.**
**Environmental fate**
**Mutagenicity**
**Phys./Chem. tests**
**Toxicology**

DATE OF INSPECTION

**2nd December 2002**

A general inspection for compliance with the Principles of Good Laboratory Practice was carried out at the above laboratory as part of UK GLP Compliance Programme.

At the time of the inspection no deviations were found of sufficient magnitude to affect the validity of non-clinical studies performed at these facilities.

Roger G. Alexander
13/2/03

Dr. Roger G. Alexander
Head, UK GLP Monitoring Authority